REMARKS

The specification has been amended on page 13 by adding paragraphs 0034 and 0035 to recite the information regarding the deposit of hybridomas producing certain monoclonal antibodies described in the application as filed and deposited in accord with Budapest Treaty requirements. Attention is directed to the Statement of Permanence and Availability of Deposited Hybridomas, attached as Exhibit 1. No new matter is added by this amendment to the specification.

Upon entry of this amendment, claims 1, 8 and 15-17 will be pending and under consideration.

Claims 1 and 8 have been amended. In particular, claim 1 has been amended to recite a method for treating an inflammatory disease of a warm-blooded living being, comprising administering to said being, in a quantity effective for said treatment, a drug comprising a substance that specifically recognizes the extracellular domain of SIRP (anti-SIRP substance) and that inhibits the functioning of macrophages by suppressing their activation by a factor of at least 10 as measure by each of the following macrophage activity tests: (i) the production of nitric oxide (NO), (ii) the production of reactive oxygen species, and (iii) the production of tumor necrosis factor-alpha (TNF-α), said anti-SIRP substance selected from Fab-fragments of monoclonal antibodies and (bio) chemically modified products of such fragments wherein the intended anti-SIRP activity has been maintained. Claim 8 has been amended to insert the Accession Numbers assigned to the deposited hybridomas producing the recited monoclonal antibodies.

Claims 15-17 have been added. Support for claim 15 is found in the specification, *inter alia*, at page 3, paragraphs 0007 and 0008. Claim 16 is directed to subject matter that was removed from claim 1 by the amendment made herein. Support for the subject matter of claim 16 is found in the specification as filed, in particular at page 3, paragraph 0008 and page 4, paragraph 0010. Support for claim 17 is found at page 7, paragraph 0016. None of the amendments to these claims limit the scope of the claimed subject matter, nor is new matter added by the amendments to the claims.

Rejections under 35 U.S.C. § 112, First Paragraph

A. Claim 8 is rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that an affidavit or declaration by Applicants, or statement by an attorney of record is required to assure that the monoclonal antibodies recited in claim 8 will be irrevocably and without

restriction released to the public upon the issuance of a patent. Applicants respectfully direct the Examiner's attention to the attached Statement of Permanence and Availability of Deposited Hybridomas ("Statement"; Exhibit 1), which attests to the deposit of the hybridomas secreting the monoclonal antibodies under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, in compliance with the criteria set forth by 37 C.F.R. §§ 1.801-1.809. Accordingly, the Statement obviates the Examiner's rejection based on the availability of the monoclonal antibodies recited in claim 8.

B. Claims 1 and 8 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, allegedly, contains subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record. Applicants respectfully disagree.

Preliminarily, Applicants note that claim 1 has been amended to recite solely a method of treating an inflammatory disease by administering an anti-SIRP substance selected from Fab-fragments of monoclonal antibodies and (bio) chemically modified products of such fragments wherein the intended anti-SIRP activity has been maintained. Claim 16 has been added, which recites solely a method of treating myeloid leukemia by administering an anti-SIRP substance selected from Fab-fragments of monoclonal antibodies and (bio) chemically modified products of such fragments wherein the intended anti-SIRP activity has been maintained.

Applicants note that under 35 U.S.C. § 112, a patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223 24, 169 U.S.P.Q. 367, 369 70 (C.C.P.A. 1971). The claimed invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir.

1988); *In re Jackson*, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

Applicants respectfully submit that the Examiner has not shown that one skilled in the art would have had to engage in undue experimentation in order to practice the claimed methods. The rejection is unsound as the Examiner provides only conclusory statements that the claimed invention is not properly supported. The Examiner cites to Gura for the fact that cancer treatment is unpredictable; however, the Examiner fails to provide any link that any of the data presented in the application, in previous responses and in the response herein, are not reasonably predictive of methods for treating an inflammatory disease or for treating myeloid leukemia using an anti-SIRP monoclonal antibody or fragment thereof. There is no requirement in Section 35 of the United States Code, of Title 37 of the Code of Federal Regulations or in the case law that requires *in vivo* data for the enablement of a claim directed to a method of treatment of a disease.

Additionally, Applicants invite the Examiner's attention to Figures 1A, 1B and 2 on Exhibit 2, which show that Fab fragments of ED9 effectively inhibit the growth/division of human myeloid leukemia cells expressing a chimeric SIRP protein, which chimera is depicted in Figure 1A. The encoding construct of the chimeric protein was expressed in human myeloid leukemia cell line THP-1 using a retroviral vector. The cells were then cultured overnight with or without a Fab fragment of ED9 and ^{3}H-thymidine incorporation was measured. As demonstrated in Figure 1B, those cells expressing the chimeric SIRP protein and in contact with the Fab fragment did not grow. Further, it is well know in the art that the growth, survival and differentiation of normal myeloid cells is in part controlled by cell-cell interactions, in particular with bone marrow stroma. Myeloid leukemia cells have a reduced ability to bind to stromal cells and that this reduced ability to bind is thought to contribute to the pathogenesis of leukemia. The chimeric protein depicted in Figure 1A was expressed in the THP-1 cell line and such cells were incubated with an Fab fragment of ED9. As depicted in Figure 2, the presence of the Fab fragment restored the adhesion of the leukemia cells to each other, which is believed to have a beneficial effect. Applicants submit that these *in vitro* assays are reasonably predictive as to whether or not an anti-SIRP substance can inhibit the growth of myeloid leukemia cells, and, thus, treat myeloid leukemia.

With regard to the Examiner's citation to Seiffert *et al.*, the fact that some leukemia cells that do not express SIRP would not respond to an anti-SIRP substance does not mean that those leukemia cells that express SIRP would not respond. An invention meets the standard for

successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 977 F.2d 1555, 24 U.S.P.Q.2d 1401, 1412 (Fed. Cir. 1992). The claimed invention is not totally incapable of achieving a useful result, thus the standard for Section 112 has been met. Further, Applicants submit that only routine experimentation using methods commonly known in the art would allow one of ordinary skill to determine whether the leukemia cells express SIRP or not, *e.g.*, by using an antibody such as ED9 or ED17 in an immunoassay. An invention is enabled when the amount of experimentation required to practice the invention is routine and where the methods are well known in the art. Such methods are well known in the art.

Further, the Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence. The facts of the present invention are similar to *Brana* in that the Examiner has not offered any reason to doubt the data in the specification or that the *in vitro* data presented herein is not reasonably predictive of treating an inflammatory disease or treating myeloid leukemia.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441.

In the *Brana* situation, the Court found that the Patent and Trademark Office had not met its initial burden. Further, the Court held that even if the Patent and Trademark Office had met its burden, the evidence proffered was clearly sufficient to meet the statutory requirement. As explained by the Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *Id.* at 1442 [quoting *In re Krimmel*, 292 F.2d 948, 953 (C.C.P.A. 1961)].

The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug for consumption. *Id.* at 1442; *see, Scott v. Finney*, 34 F.3d 1058, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.
> *Id.* at 219 (emphasis in the original).

In view of the above remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully practice the claimed methods, *i.e.*, treating

an inflammatory disease or treating myeloid leukemia with an anti-SIRP substance, without undue experimentation. This rejection under Section 112, therefore, should be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history present application. Applicants submit that the presently pending claims meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 326-3921 if any questions or issues remain.

Respectfully submitted,

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Enclosures